Doc Code: AP.PRE.REQ

PTO/SB/33 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): TTP 2002-08-US-A

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
10/777,488	February 12, 2004

First Named Inventor: Adnan M.M. Mjalli

Art Unit	Examiner
1626	Stockton, Laura L.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 50,990.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Ben Schroeder
Signature

T. Benjamin Schroeder
Typed or printed name

336/607-7300
Telephone number

April 21, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Mjalli, Adnan et al.	Examiner:	Stockton, Laura L.
Application No.:	10/777,488	Group Art Unit:	1626
Filing Date:	February 12, 2004	Confirmation No.:	2347

Title: SUBSTITUTED AZOLE DERIVATIVES AS THERAPEUTIC AGENTS

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW – Supplemental Pages

The following is intended to be in compliance with the program guidelines set forth in the July 12, 2005 Official Gazette Notice and is submitted with a Notice of Appeal. The undersigned requests careful consideration of the errors identified herein.

Rejection of claims 1-4, 7-12, and 16-25

Claims 1-4, 7-12, and 16-25 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for claiming solvates of the compounds of the claimed invention.

Standard for showing lack of Enablement

The standard for determining whether a claim is enabled is whether one can practice the claimed invention without undue experimentation. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The *Wands* factors are factors that are to be considered to determine whether a claim is enabled. No one *Wands* factor can be used by itself to assert that a claim is not enabled. Rather, it is the totality of the *Wands* factors that determine whether a claim is enabled or not.

Solvates are Enabled

When one analyzes the totality of the *Wands* factors, one can only conclude that solvates of the compounds of the present invention are enabled. The eight Wands factors are: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working

examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicants agree with the Examiner's analysis regarding some of the above factors and disagree to different degrees with the analysis of the other factors. For example, Applicants agree that the nature of the invention involves the chemical synthesis of solvates but additionally submit that the nature of the invention involves some experimentations. Applicants also agree with the Examiner that the level of one of ordinary skill in the art would be at least an experienced process chemist with a BS chemistry degree. However, Applicants believe that the Examiner mischaracterizes to varying degrees the other factors. For example, although the breadth of the claims includes presently unknown compounds embraced by the term solvates, Applicants have provided general synthetic routes to a plurality of compounds including the exact syntheses of 375 compounds many of which fit within the scope of the claims. These compounds serve as starting points for generating solvates. The formation of solvates from known compounds does not require undue experimentation and this is supported by the plurality of references that predate the filing date of the instant application and that have been supplied by Applicants to the Examiner.

Accordingly, Applicants believe perhaps the greatest mischaracterization of the various factors by the Examiner involves the state of the prior art. Although Applicants do not disagree that there is some unpredictability in chemical syntheses of solvates, the level of unpredictability in making solvates is not so high as to require undue experimentation. The generation of a solvate in most instances involves the recrystallization of a known compound in an appropriate solvent and then testing to ascertain if a solvate is generated. Applicants have provided five references that predate the present invention that explain in detail how one would go about making solvates. These references are: Caira, Vippagunta, Guillory, Byrn, and Morissette[1]. These references explain to various degrees how one would test for solvates, how one would pick the appropriate solvents for generating solvates, and also provide examples of different solvates that have been produced from known compounds. Applicants submit that because detailed synthetic procedures for 375

[1] Detailed descriptions of the teachings of these references was provided in responses to the various office actions. Due to space limitations imposed regarding the length of this document, those detailed teachings are not repeated here.

compounds and general synthetic schemes for a plurality of other compounds have been provided, most of which fit within the scope of the claims in the instant application, there are a vast array of potential starting material compounds that can be used to generate solvates of these compounds. The process of going from a known compound to generating a solvate of that compound does not involve undue experimentation. It merely involves the selection of the appropriate solvent, recrystallization in that solvent, and then screening/testing to ascertain if a solvate has been generated. The above cited references describe these processes.

On page 6 of the January 26, 2009 Office Action, the Examiner asserted that the specification merely mentions the Applicants' intention to make solvates, without teaching the preparation thereof. Applicants point out that it is well settled law that one need not disclose, and preferably omits that which is well known in the art. Please note *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986) and a series of cases that hold similarly. In light of the references referred to above and provided to the Examiner, Applicants submit that because methods used to generate solvates is well known in the art, Applicants do not need to provide further detail in the written description about how to generate solvates.

The Examiner also states that no working examples are provided. The Examiner cites a passage from *Morton International Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464 (Fed Cir. 1993) to support the proposition that because the specification shows no evidence of formation of or actual existence of solvates, Applicants must show formation of solvates or limit the claims accordingly.

The quote that the Examiner cites from *Morton* is taken out of context. In *Morton*, there was considerable evidence that the compounds that were being claimed could not be generated by the procedure outlined in the specification (i.e., the compounds could not be made). This is vastly different from the instant case where the Examiner has provided no evidence that solvates of the claimed compounds can not be made.

The one literature reference on which the Examiner does rely (i.e., Vippagunta) is ambiguous as to whether solvate formation is predictable or not. Vippagunta states:

> *Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult.*

The Examiner has used this passage to show that solvate formation is unpredictable. First, Applicants note that predictability is only one of the *Wands* factors to consider in determining whether the claims are enabled or not. Predictability, by itself, is not dispositive of enablement. Moreover, this statement from Vippagunta states nothing about whether this alleged unpredictability would make the experimentation required to generate solvates undue. Simply because something has some unpredictability, it does not mean it is not enabled.

Second, Vippagunta, in another passage, states:

> *The recent developments in computational chemistry allow the prediction of possible polymorphic forms based only on the molecular structure of the drug. The Polymorph Predictor, from Molecular Simulations, is currently the only commercial software package that can predict the possible polymorphs of an organic compound from its molecular structure. (See page 11, right hand column). . . This method has been successfully employed to generate known polymorphs of primidone . . .. and progesterone*

Here, Vippagunta has acknowledged that there is some predictability to deducing possible polymorphic structures if the molecular structure is known. Vippagunta also points out that there was commercial software available at least in 2001 that allowed one to predict the polymorphs that can be made if the structure was known. Applicants in the present case do know the molecular structures of the claimed compounds. Moreover, Vippagunta also discloses that the software package that has been used to predict the solvate structure in the formation of solvates of several compounds was known when the present application was filed. Thus, when Vippagunta is viewed as a whole, one can only come to the conclusion that Vippagunta acknowledges that there is some predictability to the formation of solvates.

The Examiner also asserts that the lack of working examples also supports a lack of enablement. However, courts have held that there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 422 F.2d 904, 951, 164 USPQ 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 USPQ 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various solvates of a particular organic molecule using routine screening methods alluded to above, no working example is necessary to enable the invention.

Applicants note the similarities of the facts associated with the presently claimed invention to the facts in *Wands*. The issue in *Wands* was whether the patentee had adequately enabled one skilled in the art to make high-affinity IgM antibodies against HbsAg that were needed to practice the claimed assay methods. *See Wands*, 858 F.2d at 735. The PTO had rejected the method claims as not being enabled for the reason that the production of high-affinity IgM anti-HbsAg antibodies was unpredictable and unreliable, thus requiring undue experimentation. *Id.* However, the Federal Circuit reversed and made the point that even though screening for hybridomas was labor-intensive with numerous steps (*e.g.*, immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells, cloning the hybridoma, screening the resulting antibodies, etc.), all the methods needed to practice the invention were well known, and the amount of effort was not excessive enough to be undue despite any unpredictability associated with making antibodies. *See id.* at 740. Applicants submit that there are more major steps involved in the production of a monoclonal antibody than in the number of steps involved in making a solvate.

Moreover, Applicants submit that the Examiner cites insufficient evidence to support a *prima facie* case of non-enablement. As explained above and in the Applicants' previous responses, the methods of making and characterizing solvates are well known, available, and routine. Accordingly, any unpredictability associated with solvate formation that might exist is clearly outweighed by the fact that preparing and screening for solvates is routine and employs well known methods.

Finally, Applicants point out that there are a plurality of companies that advertise that they can make and screen for solvates when the compounds are known. Applicants thus submit that solvates can be made without undue experimentation. These solvates can without undue experimentation be tested for activity using the biological assay described beginning at page 315 of the present written description. Accordingly, Applicants submit that the solvates of the present invention can be made and used without undue experimentation. Withdrawal of the rejection of claims 1-4, 7-12, and 16-25 as allegedly not being enabled for claiming solvates is warranted and respectfully requested.